# Complete Summary

## GUIDELINE TITLE

Guidelines for the treatment of autoimmune neuromuscular transmission disorders.

## BIBLIOGRAPHIC SOURCE(S)

Skeie GO, Apostolski S, Evoli A, Gilhus NE, Hart IK, Harms L, Hilton-Jones D, Melms A, Verschuuren J, Horge HW. Guidelines for the treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol 2006 Jul;13(7):691-9. [78 references] PubMed

## GUIDELINE STATUS

This is the current release of the guideline.

## ** REGULATORY ALERT **

## FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse**: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- June 30, 2008, CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid): Novartis and Roche have agreed to include additional labeling revisions to the WARNINGS and ADVERSE REACTIONS sections of the Myfortic and CellCept prescribing information, based on post-marketing data regarding cases of Progressive Multifocal Leukoencephalopathy (PML) in patients treated with these drugs.
- December 12, 2007, Carbamazepine: The U.S. Food and Drug Administration (FDA) has provided recommendations for screening that should be performed on specific patient populations before starting treatment with carbamazepine.
- October 29, 2007, CellCept (mycophenolate mofetil): Roche has agreed to include additional labeling revisions to the BOXED WARNING, WARNINGS/Pregnancy and Pregnancy Exposure Prevention, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Postmarketing Experience sections.

## COMPLETE SUMMARY CONTENT

## SCOPE

### DISEASE/CONDITION(S)

Autoimmune neuromuscular transmission disorders:

- Myasthenia gravis
- Lambert-Eaton myasthenic syndrome
- Neuromyotonia

### GUIDELINE CATEGORY

Treatment

### CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Oncology

### INTENDED USERS

Physicians

### GUIDELINE OBJECTIVE(S)

To review the available literature and provide evidence-based guidelines for the treatment of autoimmune neuromuscular transmission (NMT) disorders

### TARGET POPULATION

Patients with autoimmune neuromuscular transmission (NMT) disorders

### INTERVENTIONS AND PRACTICES CONSIDERED

#### Treatment

1. Myasthenia gravis
    - Acetylcholine esterase inhibitors

- Short-term plasma exchange treatment
- Intravenous immunoglobulin (IvIg)
- Thymectomy
- Oral corticosteroids (with a bisphosphonate and antacid)
- Azathioprine
- Other immunosuppressants

2. Lambert-Eaton myasthenic syndrome
    - 3,4-diaminopyridine with or without pyridostigmine
    - IvIg
    - Treatment of the underlying tumor
    - Immunosupressive treatment
3. Neuromyotonia
    - Antiepileptic drugs
    - Treatment of the underlying tumor
    - Immunomodulatory therapies

### MAJOR OUTCOMES CONSIDERED

- Effectiveness of treatment in improving muscle strength and achieving remission and steroid sparing effect
- Side effects of therapy

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE 1966–2004 and EMBASE 1966–2004 were examined with appropriate MESH and free subject terms: 1. Myasthenia, 2. Myasthenia gravis, 3. Lambert–Eaton, 4. Lambert–Eaton myasthenic syndrome/LEMS, 5. Neuromyotonia, 6. Isaacs syndrome.

The terms 1–6 were combined with the terms: 7. Treatment, 8. Medication, 9. Therapy, 10. Controlled clinical trial, 11. Randomized controlled trial, 12. Clinical trial, 13. Multicenter study, 14. Meta analysis, 15. Cross-over studies, 16. Thymectomy, 17. Immunosuppression.

The Cochrane Central Register of Controlled Trials (CENTRAL) was also sought. Articles in English that contained data which could be rated according to the guidance statement for neurological management guidelines of European Federation of Neurological Societies (EFNS) were included.

Information from patient and other voluntary organizations and existing guidelines including those from the American Academy of Neurology was reviewed and validated according to the above criteria. Finished and ongoing Cochrane data based projects on Lambert-Eaton myasthenic syndrome (LEMS) treatment,

immunosuppressive myasthenia gravis (MG) treatment, intravenous immunoglobulin (IvIg) for MG, plasmapheresis for MG and corticosteroids for MG in addition to thymectomy (TE) for MG were reviewed.

**NUMBER OF SOURCE DOCUMENTS**

Not stated

**METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Weighting According to a Rating Scheme (Scheme Given)

**RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

**Evidence Classification Scheme for a Therapeutic Intervention**

**Class I**: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

**Class II**: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

**Class III**: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

**Class IV**: Evidence from uncontrolled studies, case series, case reports, or expert opinion

**METHODS USED TO ANALYZE THE EVIDENCE**

Systematic Review

**DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

Not stated

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Four members of the task force prepared parts of the manuscript and draft statements about the treatment of myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS) and neuromyotonia. Evidence was classified as class I to IV and recommendations as level A to C according to the scheme agreed for European Federation of Neurological Societies (EFNS) guidelines (see the "Availability of Companion Documents" field in this summary). When only class IV evidence was available but consensus could be reached the Task Force has offered advice as good practice points. The statements were revised and collated into a single document, which was then revised iteratively until consensus was reached.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

### Rating of Recommendations

**Level A rating** (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

**Level B rating** (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

**Level C rating** (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

**Good practice point** When only class IV evidence was available but consensus could be reached the Task Force has offered advice as good practice points.

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see "Availability of Companion Documents" field).

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C, good practice point) are defined at the end of the "Major Recommendations" field.

#### Myasthenia Gravis

After the diagnosis of myasthenia gravis (MG) is established, an acetylcholine esterase inhibitor should be introduced. Thymoma patients should have thymectomy (TE). Acetylcholine receptor (AChR)-antibody positive early-onset patients with generalized MG and insufficient response to pyridostigmine therapy should be considered for TE, ideally within 1 year of disease onset. Immunosuppressive medication should be considered in all patients with progressive MG symptoms. The Task Force members recommend starting with prednisolone covered by bisphosphonate and antacid. If long-term treatment with steroids is expected, a steroid-sparing agent, usually azathioprine should be introduced. Non-responders or patients intolerant to this regime should be considered for treatment with one of the other recommended immunosuppressive drugs. Recommendation levels are generally **B, C or good practice points**.

#### Lambert–Eaton Myasthenic Syndrome

Evidence from small, randomized, controlled trials showed that both 3,4-diaminopyridine and intravenous immunoglobulin (IvIg) improved muscle strength scores and compound muscle action potential amplitudes in Lambert–Eaton myasthenic syndrome (LEMS) patients (**class I evidence**).

First-line treatment is 3,4-diaminopyridine. An additional therapeutic effect may be obtained if combined with pyridostigmine. If symptomatic treatment is insufficient immunosuppressive therapy should be started, usually with a combination of prednisone and azathioprine. By analogy to MG, other drugs like ciclosporin or mycophenolate can be used, although evidence of benefit is limited to case series reports (**class IV evidence**) (**level C recommendation**).

For patients with a paraneoplastic LEMS it is essential to treat the tumour. Chemotherapy is the first choice in small-cell lung cancer (SCLC) and this will have an additional immunosuppressive effect. The presence of LEMS in a patient with SCLC improves tumour survival. For a more detailed description of LEMS consult the National Guideline Clearinghouse (NGC) summary of the European Federation of Neurological Societies (EFNS) guideline, Management of Paraneoplastic Neurological Syndromes: Report of an EFNS Task Force.

#### Neuromyotonia (Peripheral Nerve Hyperexcitability)/Isaacs Syndrome

Neuromyotonia usually improves with symptomatic treatment, although evidence is case reports and case series (**class IV evidence**). Carbamazepine, phenytoin, lamotrigine and sodium valproate can be used, if necessary in combination.

Neuromyotonia often improves and can remit after treatment of an underlying cancer. In patients whose symptoms are debilitating or refractory to symptomatic therapy, immunomodulatory therapies should be tried. Plasma exchange often produces useful clinical improvement lasting about 6 weeks accompanied by a reduction in electromyography (EMG) activity and a fall in voltage-gated potassium channels (VGKC) antibody titres. Single case studies suggest that IvIg can also help. There are no good trials of long-term oral immunosuppression. However, prednisolone, with or without azathioprine or methotrexate, has been useful in selected patients (**class IV evidence**) (**good practice point**).

**Definitions**:

**Evidence Classification Scheme for a Therapeutic Intervention**

**Class I**: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

**Class II**: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

**Class III**: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

**Class IV**: Evidence from uncontrolled studies, case series, case reports, or expert opinion

**Rating of Recommendations**

**Level A rating** (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

**Level B rating** (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

**Level C rating** (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

**Good practice point** When only class IV evidence was available but consensus could be reached, the Task Force has offered advice as good practice point.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations" field).

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate treatment of autoimmune neuromuscular transmission disorders

### POTENTIAL HARMS

#### Adverse Effects of Medications

- *Acetylcholine esterase inhibitors* are usually well tolerated at standard doses of up to 60 mg five times per day. Adverse effects are caused by the increased concentration of acetylcholine (ACh) at both nicotinic and muscarinic synapses. The common muscarinic effects are gut hypermotility (stomach cramps, diarrhoea), increased sweating, excessive respiratory and gastrointestinal secretions and bradycardia. The main nicotinic adverse effects are muscle fasciculations, and sometimes, cramps.
- *Steroids* have side-effects including weight gain, fluid retention, hypertension, diabetes, anxiety/depression/insomnia/psychosis, glaucoma, cataract, gastrointestinal haemorrhage and perforations, myopathy, increased susceptibility to infections and avascular joint necrosis. The risk of osteoporosis is reduced by giving bisphosphonate, and antacids may prevent gastrointestinal complications.
- *Azathioprine* is usually well tolerated but idiosyncratic flu-like symptoms or gastrointestinal disturbances including pancreatitis occur in 10%, usually within the first few days of treatment. Some patients develop hepatitis with elevations of liver enzymes. Leucopenia, anaemia, thrombocytopenia or pancytopenia usually respond to drug withdrawal. Blood cell effects and hepatitis often do not recur after cautious reintroduction of the drug. Careful monitoring of full blood cell count and liver enzymes is mandatory and the dosage should be adjusted according to the results. About 11% of the population are heterozygous and 0.3% homozygous for mutations of the thiopurine methyltransferase gene and have an increased risk of azathioprine-induced myelosuppression.

- The relative high risk of toxicity including bone marrow suppression, opportunistic infections, bladder toxicity, sterility and neoplasms, limits the use of *cyclophosphamide* to myasthenia gravis patients.
- *Ciclosporin* has significant side-effects of nephrotoxicity and hypertension and should be considered only in patients intolerant or unresponsive to azathioprine.

### Adverse Effects of Thymectomy

Perioperative morbidity is very low and consists of wound healing disorders, bronchopneumonia, phrenic nerve damage, and sternum instability with transsternal procedures.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

*Methotrexate* and *mycophenolate mofetil* should not be given in pregnancy as no safety data are available.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better
Living with Illness

## IOM DOMAIN

Effectiveness

# IDENTIFYING INFORMATION AND AVAILABILITY

## BIBLIOGRAPHIC SOURCE(S)

Skeie GO, Apostolski S, Evoli A, Gilhus NE, Hart IK, Harms L, Hilton-Jones D, Melms A, Verschuuren J, Horge HW. Guidelines for the treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol 2006 Jul;13(7):691-9. [78 references] PubMed

## ADAPTATION

Not applicable: The guideline was not adapted from another source.

## DATE RELEASED

2006 Jul

## GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

## SOURCE(S) OF FUNDING

European Federation of Neurological Societies

## GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force on the Treatment of Autoimmune Neuromuscular Transmission Disorders

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

None of the Task force members reported any conflicts of interest.

## GUIDELINE STATUS

This is the current release of the guideline.

## GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site.

Print copies: Available from Dr Geir Olve Skeie, Department of Neurology, Haukeland University Hospital, 5021 Bergen, Norway; Phone: +47 55 97 5000; Fax: +47 55 97 5165; E-mail: geir.olve.skeie@helse-bergen.no

## AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site.
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the European Federation of Neurological Societies Web site.

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on April 9, 2007. The information was verified by the guideline developer on May 15, 2007. This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on CellCept (mycophenolate mofetil). This summary was updated by ECRI Institute on January 10, 2008, following the U.S. Food and Drug Administration advisory on Carbamazepine. This summary was updated by ECRI Institute on July 8, 2008, following the updated U.S. Food and Drug Administration (FDA) advisory on CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid).

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